Amendments to the Specification

Please delete the previously filed Sequence Listing and insert the substitute Sequence Listing filed herewith.

Amendment to the Claims

Please amend claims 32, 33 and 78 as indicated in the listing of claims.

Claims 1-31, 34-35, 38-40, 58-73 and 76 were previously canceled without prejudice or disclaimer.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims

1.- 31. (Canceled).

32. (Currently amended) A method of identifying an agent that affects isopeptidase activity of a polypeptide comprising:

incubating a test agent with a Rpn11 polypeptide in the presence of a modifier protein and a target protein, ~~comprising~~ wherein the Rpn11 polypeptide has a Jab1/Mpn/Mov34 Metalloenzyme (JAMM) domain consisting essentially of an amino acid sequence of HXHXXXXXXXXXXD (SEQ ID NO:1), wherein H is histidine, D is aspartate, and X is any amino acid, and wherein the polypeptide having isopeptidase activity deconjugates a modifier protein from a target protein by cleaving a peptide bond formed between the carboxy terminus of the modifier protein and a free amino group of the target protein in proximity to a metal ion; and

determining the isopeptidase activity of the test agent by measuring deconjugation of the modifier protein from the target protein in the presence and absence of the test agent, wherein a difference in the[[-]] isopeptidase activity in the presence versus the absence of the test agent is indicative of an agent[[-]] that affects[[-]] isopeptidase activity of the Rpn11 polypeptide, and wherein the Rpn11 polypeptide is ~~Rpn11~~ as set forth in SEQ ID NO:23 or 24~~(Accession Nos.: NP_116659; NP_005796; and O00487), or Rpn11 complex~~.

33. (Currently amended) The method of claim 32, wherein the JAMM domain consists essentially of an amino acid sequence of GW(Y/I)H(S/T)HPXXXXXXSXXD [[(]] as set forth in SEQ ID NO. 2[[)]], wherein G is glycine, W is tryptophan, Y is tyrosine, I is isoleucine, H is histidine, S is serine, T is threonine, P is proline, D is aspartate, X is any amino acid, Y/I is either Y or I, and S/T is either S or T.

34. – 35. (Canceled).

36. (Original) The method of claim 32, wherein the target protein has ubiquitin ligase activity.

37. (Original) The method of claim 32, wherein the target protein is part of a protein complex having ubiquitin ligase activity.

38. – 40. (Canceled).

41. (Previously presented) The method of claim 32, wherein an increase in the amount of the target protein not conjugated to the modifier protein is indicative of an agent that increases deconjugation of the modifier protein from the target protein.

42. (Original) The method of claim 32, wherein the target protein has the activity of peroxidase, alkaline phosphatase, or luciferase.

43. (Original) The method of claim 32, wherein the target protein is a fluorescent protein.

44. (Original) The method of claim 43, wherein the fluorescent protein is selected from the group consisting of green fluorescent protein, yellow fluorescent protein, cyan fluorescent protein and dsRed.

45. (Original) The method of claim 43, wherein the target protein is a fluorescent protein via chemical modification.

46. (Original) The method of claim 32, wherein the target protein causes production of a detectable signal upon deconjugation from the modifier protein.

47. (Previously presented) The method of claim 32, wherein Rpn11 is a polypeptide complex of 26S proteasome.

48. (Previously presented) The method of claim 32, wherein Rpn11 is a polypeptide complex of 26S proteasome and the modifier protein is an ubiquitin.

49. (Original) The method of claim 47, wherein the incubation is conducted in the presence and absence of the test agent, the target protein, the 26S proteasome, and a 20S inhibitor.

50. (Original) The method of claim 47, wherein the incubation is conducted in the presence and absence of the test agent, the target protein, the 26S proteasome, a 20S inhibitor, and ATP.

51. (Original) The method of claim 50, wherein the incubation further includes an inhibitor of deubiquitination by an ubiquitin isopeptidase.

52. (Original) The method of claim 47, wherein the target protein not conjugated to the modifier protein is not degraded.

53. (Original) The method of claim 47, wherein the target protein is Sic1.

54. (Original) The method of claim 47, wherein the 26S proteasome is purified from *S. cerevisiae*.

55. (Original) The method of claim 47, wherein the 26S proteasome is purified from eukaryotic cells.

56. (Original) The method of claim 47, wherein the 26S proteasome is purified from human cells.

57. (Original) The method of claim 32, wherein the test agent is a member of a compound library selected from the group consisting of hydroxamate compound library, reverse hydroxamate compound library, carboxylate compound library, thiol compound library, and phosphonate compound library.

58. -73. (Canceled).

74. (Previously presented) The method of claim 32, wherein the method further comprises carrying out the incubation in the presence of an inhibitor of degradation of the target protein.

75. (Previously Presented) The method of claim 32, further comprising after the incubation, determining whether the modifier protein remains conjugated to the target protein via a peptide bond formed between the carboxy terminus of the modifier protein and a free amino group of the target protein.

76. (Canceled).

77. (Currently amended) The method of claim ~~32~~ 78, wherein the polypeptide comprising the JAMM domain comprises AMSH1 and/or AMSH2.

78. (Currently amended) A method of identifying an agent that affects isopeptidase activity of a polypeptide comprising:

incubating a test agent with a AMSH polypeptide in the presence of a modifier protein and a target protein, wherein the AMSH polypeptide has ~~comprising~~ a Jab1/Mpn/Mov34 Metalloenzyme (JAMM) domain consisting essentially of an amino acid sequence of HXHXXXXXXXXXXD (SEQ ID NO:1), wherein H is histidine, D is aspartate, and X is any amino acid, and wherein the AMSH polypeptide having isopeptidase activity deconjugates a modifier protein from a target protein by cleaving a peptide bond formed between the carboxy terminus of the modifier protein and a free amino group of the target protein in proximity to a metal ion; and

determining the isopeptidase activity of the test agent[[_]] by measuring deconjugation of the modifier protein from the target protein in the presence and absence of the test agent, wherein a difference in the[[-]] isopeptidase activity in the presence versus the absence of the test agent is indicative of an agent[[-]] that affects[[-]] isopeptidase activity of the polypeptide, and wherein the AMSH polypeptide is AMSH as set forth in SEQ ID NO:7 ~~(Accession No.: JC7982 and AAD05037)~~.